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Systemic Hemophagocytosis Masking the Diagnosis of Large Cell Non-Hodgkin Lymphoma

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An 11-year-old female presented with clinical features suggestive of malignant histiocytosis: fever, weight loss, subcutaneous nodules, pulmonary infiltrates, adenopathy, and hepatosplenomegaly. On biopsy, lymph node and bone marrow demonstrated necrosis and extensive hemophagocytosis with no definitive evidence of malignancy; the subcutaneous nodules, however, demonstrated large-cell non-Hodgkin lymphoma. This clinicopathologic picture has been reported in adults, but not in children. Although serum G-CSF, M-CSF, and TNF levels were not elevated in this child, it is possible that other cytokines induced either directly or indirectly by the subcutaneous lymphoma resulted in hemophagocytosis. Med. Pediatr. Oncol. 29:167–169, 1997. © 1997 Wiley-Liss, Inc.

INTRODUCTION

Disseminated malignant histiocytosis (MH) is a clinicopathologic entity characterized clinically by fever, weight loss, subcutaneous nodules, pulmonary infiltrates, adenopathy, and hepatosplenomegaly; the pathologic features include infiltration of lymph nodes by ''malignant'' histiocytes and other inflammatory cells [1]. Some cases have an associated (2;5)(p23;q35) translocation, like that described in CD30+ anaplastic large cell lymphomas, leading to speculation that most previously described cases of MH are actually large cell lymphomas [2,3,4]. In this regard, other subtypes of large cell lymphoma have also been reported to mimic MH on the basis of both pathologic and clinical features [5–10]. For example, Gonzalez et al. reported a clinicopathologic syndrome in adults which included subcutaneous large cell lymphoma associated with systemic hemophagocytosis, mimicking MH [10]. Here we report, to our knowledge, the first case of a child with the clinicopathologic syndrome described by Gonzalez in adults.

CASE REPORT

H.C., an 11-year-old white female, presented with a 6-week history of malaise, fever, subcutaneous nodules, and enlarged right inguinal lymph node. The lymph node biopsy was interpreted as consistent with MH, for which she was referred to St. Jude Children's Research Hospital. The physical exam revealed an ill-appearing edematous female who demonstrated expiratory wheezing in all lung fields, hepatosplenomegaly, and nontender, nonerythematous subcutaneous nodules on head, trunk, and extremities. Initial laboratory findings included the following: hemoglobin, 9.6 g/dl; leukocyte count, 2.4×10^9/L (53% neutrophils, 12% bands, 33% lymphocytes, 1% myelocytes, 1% metamyelocytes); platelets, 139×10^9/L; erythrocyte sedimentation rate, 5 mm/hr; LDH, 1200 U/L; SGOT, 631 U/L; SGPT, 145 U/L; and cholesterol, 123 mg/dL. Chest X ray demonstrated a diffuse micronodular infiltrative pattern.

The inguinal lymph node biopsy revealed a histiocytic infiltrate with hemophagocytosis and massive necrosis, but no obvious malignant cells (Fig. 1); the bone marrow aspirate smears showed a prominent benign histiocytosis with erythro- and leukophagocytosis (Fig. 2). Although a diagnosis of a ''benign'' hemophagocytic syndrome was suggested from examination of this material, biopsy of the subcutaneous nodules was performed to further clarify the diagnosis. Biopsy of the nodules revealed malignant immunoblastic large cell lymphoma, extending from the subcutaneous fat into the upper dermis (Fig. 3). Immunoperoxidase stains for CD45, CD20 (L26), CD45RO (UCHL-1), S-100, CD30, ALK protein, and lysozyme in paraffin-embedded tissue were negative in the malignant cells, consistent with a non-T, non-B cell phenotype. There was insufficient fresh tissue for additional T- and B-lineage associated antigen and cytoge-

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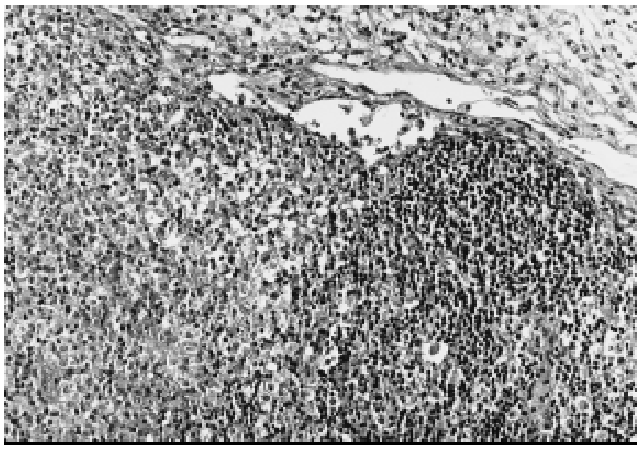

Fig. 1. Inguinal lymph node. Large portions of the lymph node contain large areas of necrosis with many histiocytes that display hemophagocytosis. An intact primary follicle is present at the upper right of the photograph. Hematoxylin and eosin stain. Original magnification: 10×.

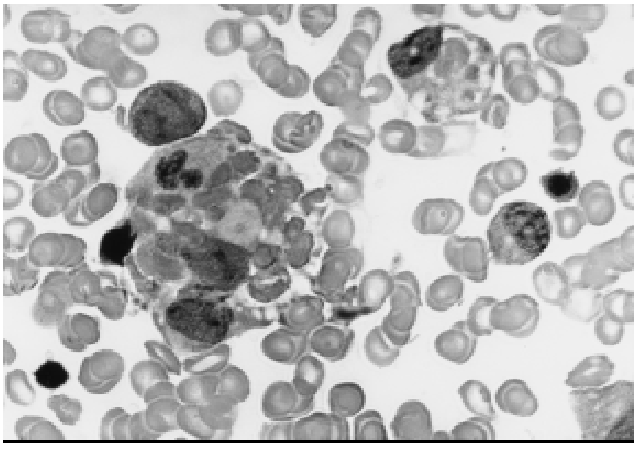

Fig. 2. Bone marrow aspirate containing many histiocytes. Shown are two histiocytes that contain phagocytized red blood cells and leukocyte nuclei. Wright stain. Original magnification: 100×.

netic studies. Polymerase chain reaction (PCR) screening for the t(2;5) in the morphologically uninvolved bone marrow at diagnosis was negative.

The patient was classified as stage III, due to multiple subcutaneous nodules, and enrolled on the St. Jude DAC protocol for large cell lymphoma. She received dexamethasone, cytarabine, carboplatin, cyclophosphamide, Adriamycin, vincristine, methotrexate, and 6-mercaptopurine delivered over a 10-month period. Approximately 36 hours into the first course of chemotherapy, the subcutaneous nodules became extremely tender and developed an erythematous border measuring approximately 3–4 cm in diameter, resembling a ''wheel and flare'' reaction. The patient concurrently became hypotensive, with an associated capillary leak syndrome similar to that observed with high-dose IL-2 administration. Within several days the capillary leak syndrome resolved, the

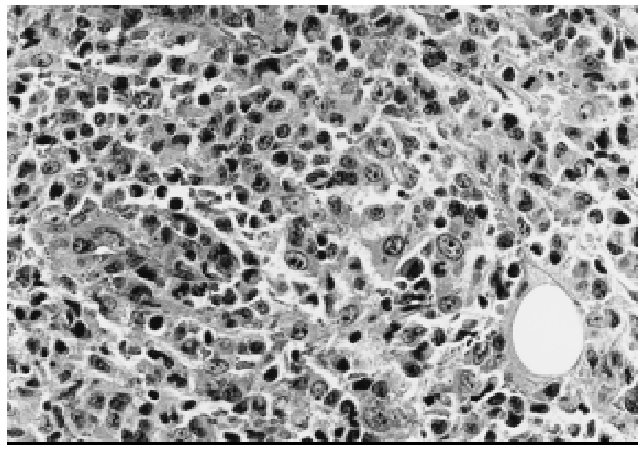

Fig. 3. Biopsy of skin nodule. The dermis and subcutaneous fat contain an infiltrate of atypical medium and large lymphoid cells. Large cells have features of immunoblasts. Hemophagocytosis is not present. Hematoxylin and eosin stain. Original magnification: 50×.

subcutaneous nodules regressed, and the local erythema and tenderness resolved. Blood cultures remained negative. G-CSF and M-CSF levels obtained prior to chemotherapy and during the hypotensive episode were not significantly elevated (<60 ng/ml and <2.5 ng/ml, respectively); nor were tumor necrosis factor (TNF) levels (<10 TNF units/ml) obtained during the hypotensive episode. The patient achieved a complete remission and remains disease free 33+ months from diagnosis—an outcome comparable to the majority of children with large cell NHL treated with modern therapy.

DISCUSSION

Large cell lymphomas have been reported to mimic the clinicopathologic entity referred to as ''malignant histiocytosis'' (MH) [5–10]. In some of these lymphoma cases, the tumor cells resemble activated histiocytes. Examples of this situation include both the anaplastic large cell lymphomas as described in the Kiel classification system and the CD30+ (recognized by Ki-1 or Ber-H2 monoclonal antibodies) immunoblastic large cell lymphomas, as defined by the National Cancer Institute Working Formulation [5,7,9]. In some settings, the lymphoma cells are phagocytic, making the distinction from MH even more challenging [6,8]. For example, Kaneko et al. reported three children with phagocytic large T-cell lymphoma of peripheral nodes that contained the t(2;5)(p23;q35) translocation [8]. In addition, Kadin et al. reported 2 adults with erythrophagocytic T-gamma lymphoma which also mimicked MH [6].

A third situation in which NHL can be confused with MH is exemplified by both our pediatric patient and the 8 adult patients (aged 19–54) described by Gonzalez et al., who presented with subcutaneous T-cell lymphoma

and associated systemic hemophagocytic syndrome mimicking MH [10]. Among the adult cases, the malignant lymphoma (diffuse, mixed small and large cell, 4 cases; large cell, immunoblastic, 4 cases) was apparently limited to the subcutaneous tissue. The distribution of erythrophagocytosis included skin (7/8), bone marrow (7/8), lymph node (5/5), spleen (4/5), liver (5/5), and lung (1/5). In our patient, erythrophagocytosis was biopsy-proven in bone marrow and clinically suspected in liver, spleen, and lung. She also had elevated liver enzyme levels, which were also documented in 4 of 8 cases by Gonzalez [10].

The pathogenesis of this clinicopathologic entity has yet to be fully elucidated. It is likely that the lymphoma cells release a cytokine that directly or indirectly stimulates normal histiocytes resulting in the associated systemic hemophagocytosis. In the supernatant of cell cultures from patients with either T-cell malignancies or angiocentric immunoproliferative lesions, Simrell et al. identified a substance that augmented the phagocytosis of IgG-coated ox red blood cells by the human monocyte/macrophage cell line U937 [11]. They speculated that this substance may play a role in the hemophagocytic syndromes associated with certain T-cell malignancies. Although our patient had clinical signs suggestive of cytokine production, none of the 3 cytokines assayed were elevated.

Our patient represents, to our knowledge, the only child with the clinicopathologic picture described in adult patients by Gonzalez. Clearly, more information is needed to fully characterize the clinical and biologic features of this entity as well as the other malignant lymphomas simulating malignant histiocytosis.

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REFERENCES

1. Zucker JM, Caillaux JM, Vanel D, Gerard-Marchant R: Malignant histiocytosis in childhood. Clinical study and therapeutic results in 22 cases. Cancer 45:2821–2829, 1980.
2. Benz-Lemoine E, Brizard A, Huret J-L, Babin P, Guilhot F, Covet D, Tanzer J: Malignant histiocytosis: A specific t(2;5)(p23;q35) translocation? Review of the literature. Blood 72:1045–1047, 1988.
3. Sandlund JT, Pui C-H, Roberts WM, Santana VM, Morris SW, Berard CW, Hutchison RE, Ribeiro RC, Mahmoud H, Crist WM, Heim M, Raimondi SC: Clinicopathologic features and treatment outcome of children with large-cell lymphoma and the t(2;5)(p23;q35). Blood 84:2467–2471, 1994.
4. Sandlund JT, Pui C-H, Santana VM, Mahmoud M, Roberts WM, Morris S, Raimondi S, Ribeiro R, Crist WM, Lin J-S, Mao L, Berard CW, Hutchison RE: Clinical features and treatment outcome for children with CD30+ large cell non-Hodgkin's lymphoma. J Clin Oncol 12:895–898, 1994.
5. Kadin ME: Ki-1-positive anaplastic large-cell lymphoma: A clinicopathological entity? J Clin Oncol 9:533–536, 1991.
6. Kadin ME, Kamoun M, Lamberg J: Erythrophagocytic Tγ lymphoma. A clinicopathologic entity resembling malignant histiocytosis. N Engl J Med 304:648–653, 1981.
7. Kadin ME, Sako D, Berliner N, Franklin W, Woda B, Borowitz M, Ireland K, Schweid A, Herzog P, Lange B, Dorfman R: Childhood Ki-1 lymphoma presenting with skin lesions and peripheral lymphadenopathy. Blood 68:1042–1049, 1986.
8. Kaneko Y, Frizzera G, Edamura S, Maseki N, Sakurai M, Komada Y, Sakurai M, Tanaka H, Sasaki M, Suchi T, Kikuta A, Wakasa H, Hojo H, Mizutani S: A novel translocation, t(2;5)(p23;q35), in childhood phagocytic large T-cell lymphoma mimicking malignant histiocytosis. Blood 73:806–813, 1989.
9. Schnitzer B, Roth MS, Hyder DM, Ginsburg D: Ki-1 lymphomas in children. Cancer 61:1213–1221, 1988.
10. Gonzalez CL, Medeiros LJ, Braziel RM, Jaffe ES: T-cell lymphoma involving subcutaneous tissue. Am J Surg Pathol 15:17–27, 1991.
11. Simrell CR, Margolick JB, Crabtree GR, Cossman J, Fauci AS, Jaffe ES: Lymphokine-induced phagocytosis in angiocentric immunoproliferative lesions (AIL) and malignant lymphoma arising in AIL. Blood 65:1468–1476, 1985.